IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Helmut Meissner *et al.* Examiner: Evelyn Mei Huang

Serial No.: 09/976,950 Group Art Unit: 1625

Filed: October 11, 2001 Docket: 1/1151

For: ANTICHOLINERGICS WHICH MAY BE USED AS MEDICAMENTS AS WELL AS PROCESSES FOR PREPARING THEM

Assistant Commissioner for Patents
Washington DC 20231

DECLARATION OF RICHARD JÁN REICHL UNDER 37 C.F.R. § 1.132

Sir:

I, Richard Ján Reichl, declare that:

1. I have studied Veterinary Medicine at the Universities of Giessen, Germany and Vienna, Austria from 1958 to 1962 (Degree: License to Practise).

2. I did my doctoral thesis in the Pharmacological Department of the Justus Liebeig University of Giessen, Germany from 1962 to 1964 and received a Ph.D. (Dr. med. vet.) from the University of Giessen, Germany in 1964.

3. Since 1967, I have been employed by Boehringer Ingelheim, presently in the Department of Pulmonary Research of Boehringer Ingelheim Pharma GmbH & Co. KG in Ingelheim am Rhein, Germany.

4. I am familiar with the above-identified patent application (hereinafter "the Meissner *et al.* application").

5. I am familiar with the U.S.P.T.O. Office Actions dated November 26, 2002, and April 11, 2003, and the prior art references cited therein: Banholzer *et al.* (U.S. Patent No. 5,770,738; hereinafter "Banholzer I") and Banholzer *et al.* (U.S. Patent No. 5,654,314; hereinafter "Banholzer II").

6. Under my responsibility and control, the bronchoprotective efficacy of scopine 2,2-diphenylpropionate-methobromide (Example 1 of the Meissner *et al.* application) and of Examples 5 and 10 of Table II of Banholzer I and Banholzer II was determined according to the experimental procedure described in ANNEX 1 (Kallos-Pagel model).

7. The experiment according to ANNEX 1 determined that Examples 5 and 10 of Table II of Banholzer I and Banholzer II in the experiment set forth in ANNEX 1 show a bronchoprotective efficacy of 100% after 20 hours at a concentration of 3 mg/mL. The experiment according to ANNEX 1 further determined that the bronchoprotective efficacy of scopine 2,2-diphenylpropionate-methobromide (Example 1 of the Meissner *et al.* application) at 3 mg/mL decreases after about 24 hours to a value of about 30%.

8. The graphic illustration of the results obtained for Example 1 of the Meissner *et al.* application and for the Examples 5 and 10 of Table II of Banholzer I and Banholzer II is depicted in ANNEX 2.

9. I hereby declare that the experimental results obtained for the tested compound according to the Meissner *et al.* application show that this compound fits into the pharmacokinetic profile necessary for a once-a-day drug, whereas the Banholzer I and Banholzer II compounds show such an extremely long duration of action that they are not useful for a once-a-day mode of administration. Furthermore, I conclude that this superiority of the Meissner *et al.* compound was neither taught, suggested, nor deducible by the cited prior art. Moreover, I conclude that these findings would have been both surprising and unexpected to one of ordinary skill in the art at the time the invention was made.

The undersigned declares further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Dated: 21. kai 2003 Signature: Richard J. Reichl

(Richard Ján Reichl)

ANNEX 1

Method for the Determination of Bronchoprotection Against Acetylcholine-Induced Bronchospastic Collapse in Guinea Pigs After Inhalative Administration of Aqueous Solutions Containing the Tested Compounds (According to the Kallos-Pagel Model)

Animals

Male guinea pigs (breed: Dunkin-Hartley, Pirbright White) were purchased from Harlan Winkelmann/Borchen, Germany. The guinea pigs were housed in single Macrolon type III cages with softwood granulate bedding (Lignocel, type ¾) purchased from Rettenmayer & Söhne, Holzmühle, Germany. The guinea pigs had free access to pelleted food (Type Ssniff/MS-Zucht 4 mm Pellets, Altromin, Lage, Germany) and drinking water in a special air conditioned animal room (temperature 23°C, humidity 44% to 45%) with a light dark cycle of 12 hours.

Spasmogen

Acetylcholine chloride was purchased from Sigma Diagnostics, St. Louis, MO, USA

Acetylcholine-Induced Bronchoconstriction

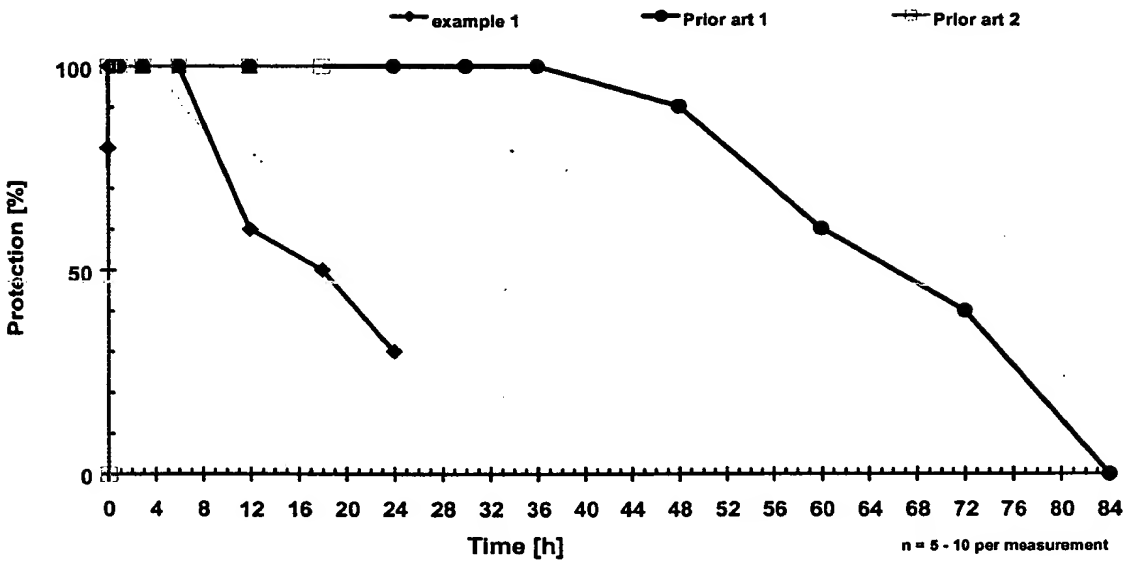
The experiments were performed using a modified method of that described by Kallos and Pagel (1937). In detail, guinea pigs were placed individually into a Plexiglas inhalation box filled with an aerosol, prepared from an 1% aqueous acetylcholine chloride solution, using a nebulizer (Inhalette, Dräger, Lübeck, Germany) with compressed air (200 kPa). The animals developed dyspnea and collapsed. Thereafter the animals were removed immediately. The time until the animals collapsed due to bronchoconstriction was recorded. The inhalation of aqueous solutions of the test compounds (3 mg/mL) was performed in the same way as described for ACh. The exposure time to anticholinergic compounds was 60 seconds. Animals were challenged with ACh aerosol at different time points after inhalation of the respective test compound. Animals which passed the threefold time interval of the corresponding control groups were recorded as protected. The percentage of protected animals was calculated.

References:

Kallos P and W Pagel (1937): Experimentelle Untersuchungen über Asthma bronchiale. Acta Medica Scandinavica 91: 292-303

ANNEX 2

Graphic Illustration of the Results Obtained According to the Kallos_Pagel Model



Legend:

example 1 is Example 1 according to the instantly claimed invention (Meissner *et al.* application) as determined according to this Declaration;

Prior art 1 is Example 10 of Table II of Banholzer I and Banholzer II as determined according to this Declaration; and

Prior art 2 is Example 5 of Table II of Banholzer I and Banholzer II as determined according to this Declaration.

Dosing: all compounds were administered at a concentration of 3 mg/mL.